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Micro fabricated devices for oral drug delivery

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Learning objectives:

1. Explain the ideas behind the use of microcontainers
2. Describe which types of compounds that can be filled into microcontainers
3. Evaluate the *in vivo* performance of microcontainers as an oral drug delivery system

INTRODUCTION: Microcontainers are polymeric, cylindrical devices in micrometer size and have been proven useful in oral drug delivery¹⁻³. The hypothesis is that oral bioavailability can be improved significantly by utilizing microcontainers loaded with drug(s) and sealed with lids protecting the drug through the gastrointestinal tract. The purpose of this work was to fabricate microcontainers from either SU-8 or from biodegradable polymers such as polycaprolactone (PCL), and to load these microcontainers with either poorly water soluble drugs or particulates. Furthermore, the aim was to investigate the application of microcontainers as oral drug delivery system in terms of release, mucoadhesion and oral bioavailability in rats.

METHODS: SU-8 microcontainers were fabricated using lithography, whereas PCL microcontainers were prepared by hot punching. Subsequently, drug was loaded into the microcontainers using a variety of technologies. The SU-8 microcontainers were filled with polyvinylpyrrolidone (PVP) followed by supercritical CO₂ impregnation of e.g. ketoprofen into the PVP matrix. As an alternative filling method, the powder of amorphous sodium salt of furosemide (ASSF) or lipid particulates with ovalbumin were filled into the SU-8 microcontainers. The PCL microcontainers were loaded with drug formulation by embossing the microcontainers into a drug/polymer layer. In most cases, an enteric-resistant lid of Eudragit L100 was spray coated onto the cavity of the microcontainers. Release of drug from the coated microcontainers was investigated using a μ -Diss profiler (Pion, USA) in simulated gastric medium at pH 2 and intestinal medium at pH 6.5. Closed loop *in situ* intestinal perfusion studies as well as *in vivo* studies in rats were performed to study the mucoadhesive effect of microcontainers and oral bioavailability of the drugs loaded into the microcontainers.

RESULTS: SU-8 microcontainers had an inner diameter of 220 μ m and a cavity depth of 270 μ m (Fig. 1a, 1b), whereas the PCL microcontainers had an inner diameter of 240 μ m and a cavity depth of 65 μ m. A fast release of ASSF (88% within 3h) or ketoprofen (100% within 6h) from the microcontainers was observed and the Eudragit coating was shown not to be a hindrance for rapid release at intestinal conditions. It was shown that the microcontainers only attached to the mucus layer in the intestine and not in the stomach. For ASSF, the microcontainers were seen to increase the relative oral bioavailability by 220% within 24h, compared to the control (Fig. 2).

CONCLUSIONS: The fabricated microcontainers show considerable future potential as oral drug delivery systems.

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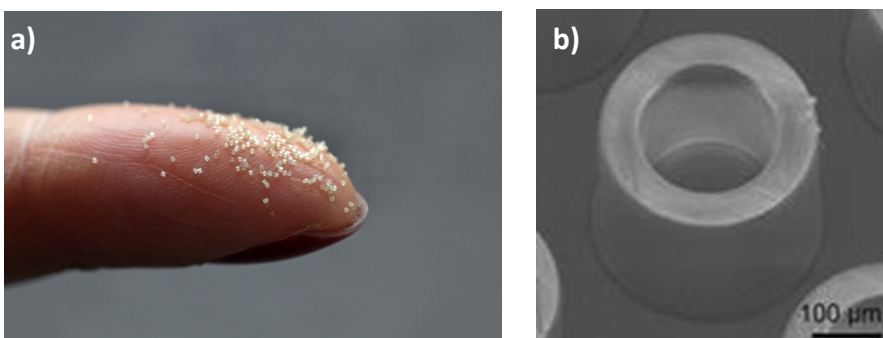


Fig 1. a) Photograph of microcontainers placed on a finger. The microcontainers have a size comparable to sugar grains. b) Image of an SU-8 microcontainer.

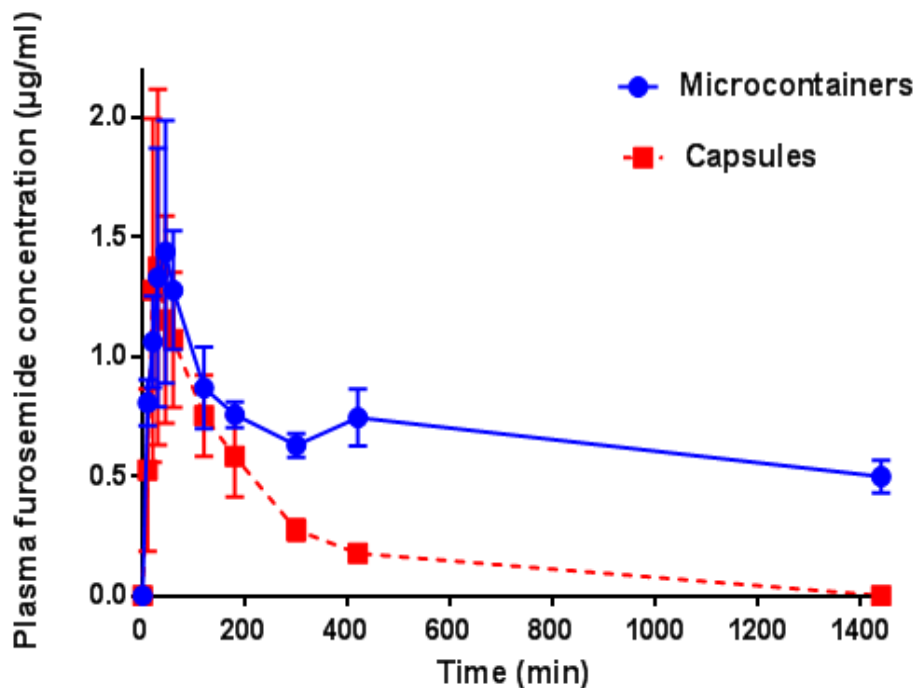


Fig. 2: Plasma concentrations of microcontainers filled with ASSF coated with Eudragit® L100 and filled into capsules and ASSF dosed in capsules with Eudragit coating after orally dosing to rats